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(incorporated in Denmark)

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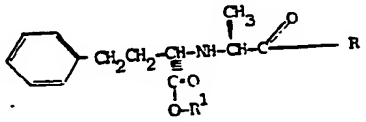
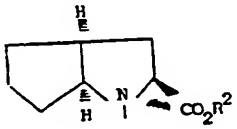
(54) N-(1-carboxy-3-phenylpropyl)alanyl derivatives

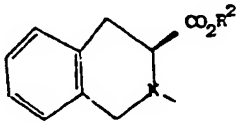
(57) Compounds which are useful in the *treatment of hypertension and congestive heart failure* have the general formula I:



in which the asymmetric centers all have the *S*-configuration, and in which R stands for

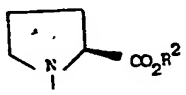


(Ia)

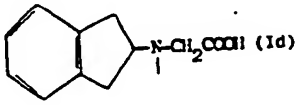


(Ic)

or

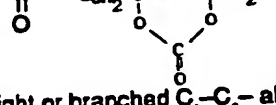


(Ib)



(Id)

and R^1 and R^2 are independently hydrogen, lower alkyl, aryl-lower alkyl, or –A–O–C–D; provided that at least one of R^1 or R^2 is –A–O–C–D; where A stands for –CH(R^3)–, –CH_2–CH(OH)–CH_2–, or



(where R^3 is hydrogen, lower alkyl or aryl-lower alkyl); lower alkyl stands for straight or branched C_1–C_6– alkyl, aryl stands for unsubstituted or substituted phenyl or naphthyl, and D–C–O– stands for the radical of a carboxy group containing compound (D–COOH) with diuretic and/or saluretic activity; and salts thereof.

The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1982.

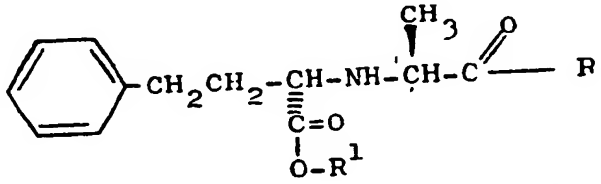
This print takes account of replacement documents submitted after the date of filing to enable the application to comply with the formal requirements of the Patents Rules 1982.

GB 2 207 129 A

CHEMICAL COMPOUNDS

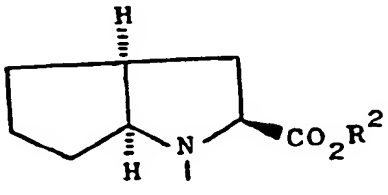
The present invention relates to hitherto unknown compounds of formula I, to salts thereof, to methods for producing said new compounds, to pharmaceutical compositions containing the new compounds, to dosage units of the compositions, and to methods for treating patients (including animals) using said new compounds and compositions.

The compounds of the invention, which are valuable in the human and veterinary practice, are represented by the general formula I:



(I)

in which the asymmetric centers all have the S-configuration, and in which R stands for



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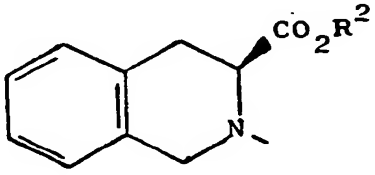

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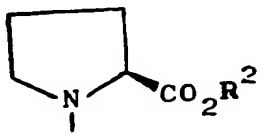
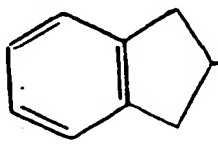
or

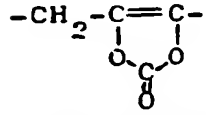


(Ib)



(Id)

and R^1 and R^2, which can be the same or different, each stands for hydrogen, lower alkyl, aryl-lower alkyl, or -A-O-C(=O)-D; provided that at least one of R^1 or R^2 is -A-O-C(=O)-D; where A stands for $-CH(R^3)-$, $-CH_2-CH(OH)-CH_2-$, or



, where R^3 is hydrogen, lower alkyl or aryl-lower alkyl; lower alkyl stands for straight or branched C_1-C_6-alkyl, aryl stands for unsubstituted or substituted phenyl or naphthyl, and D-C(=O)-O- stands for the radical of a carboxy group containing compound (D-COOH) with diuretic and/or saluretic activity. DCOO- may e.g. be derived from a sulfamoylbenzoic acid or aryloxyacetic acid diuretic, but any diuretic and/or saluretic compound containing a carboxy group may in principle form the DCOO- moiety of the compounds of formula I.

The below cited patents describe diuretics from which the DCOO-radical may be derived, this list not to be considered as limiting the scope of the present invention:

U.S. Patent No. 3,755,383

U.S. Patent No. 3,875,150

U.S. Patent No. 3,634,583

U.S. Patent No. 3,806,534

U.S. Patent No. 3,971,819

U.S. Patent No. 3,985,777

U.S. Patent No. 3,758,522

U.S. Patent No. 3,790,584

U.S. Patent No. 3,793,459

U.S. Patent No. 3,816,482

U.S. Patent No. 3,828,059

U.S. Patent No. 3,787,421

U.S. Patent No. 3,897,476

U.S. Patent No. 4,018,794

U.S. Patent No. 3,950,376

U.S. Patent No. 3,972,886

U.S. Patent No. 3,989,745

U.S. Patent No. 3,898,266

U.S. Patent No. 3,950,380

U.S. Patent No. 3,058,882

U.S. Patent No. 3,255,241

U.S. Patent No. 4,208,535

U.S. Patent No. 4,096,267

U.S. Patent No. 4,296,122

U.S. Patent No. 4,291,050

U.S. Patent No. 4,258,059

U.S. Patent No. 4,249,021

U.K. Patent No. 1,217,172

German Offenlegungsschrift No. 2,917,997

U.S.S.R. Patent No. 749,829

U.S.S.R. Patent No. 740,769

European Patent Application No. 56.970

Japanese Patent Application No. 81-83469

More particularly, R_1 and R_2 may represent hydrogen or a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl radical, one of the isomeric pentyl radicals, e.g. tert-pentyl and neopentyl, or one of the isomeric hexyl radicals, e.g. 1,2,2-trimethylpropyl or 1-methyl-1-ethylpropyl, or benzyl or phenethyl or -A-O-C(=O)-D; and R_3 stands for hydrogen or methyl.

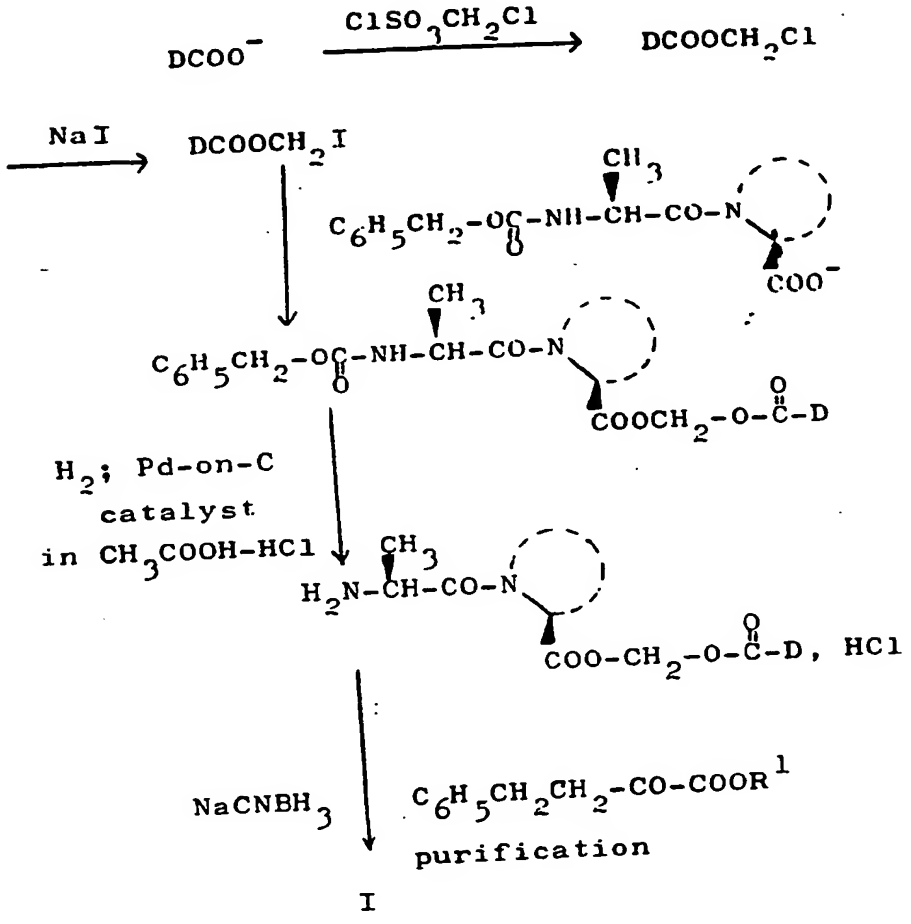
The compounds of the invention are readily absorbed after oral administration. They have a pronounced antihypertensive and diuretic effect and are in particular valuable in the treatment of hypertension and congestive heart failure.

The salts of the present compounds are primarily salts with pharmaceutically acceptable acids which form salts with the secondary amino group in the molecule. As examples of pharmaceutically acceptable, non-toxic acids which may form part of the present salts, mention may be made of e.g. hydrochloric, hydrobromic and hydroiodic acid, phosphoric acid, sulphuric acid, nitric acid, p-toluenesulphonic acid, methanesulphonic acid, formic acid, acetic acid, propionic acid, citric acid, tartaric acid, maleic acid, and pamoic acid.

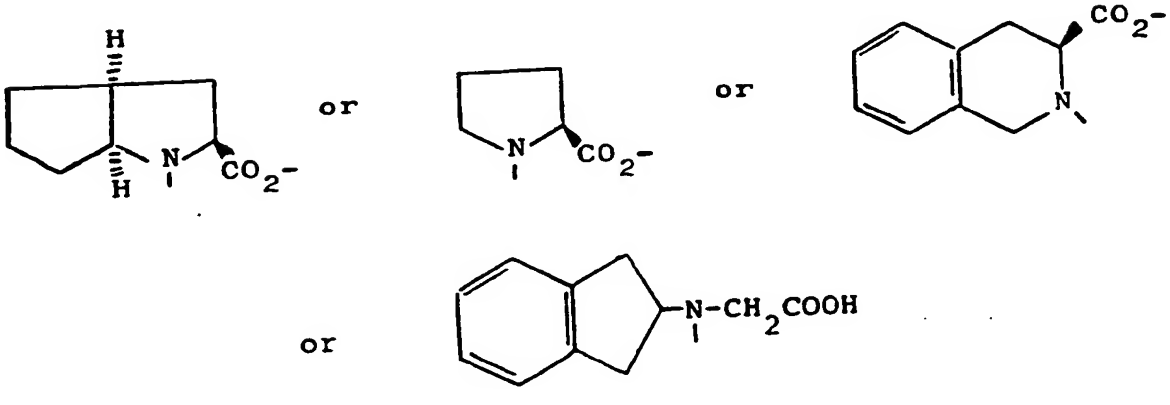
In case that R^1 or R^2 stands for hydrogen, the compounds of formula I can furthermore form salts with bases or can be used in their zwitterionic form.

The compounds of formula I can be synthesized using methods and synthetic procedures well known to the man

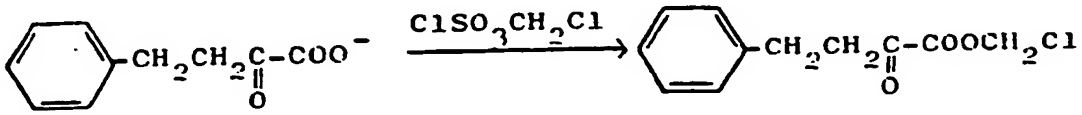
skilled in the art. In one method, a compound of formula I in which R^2 stands for $-CH_2-O-\overset{O}{\overset{\|}{C}}-D$ can e.g. be synthesized by the following sequence of reactions:

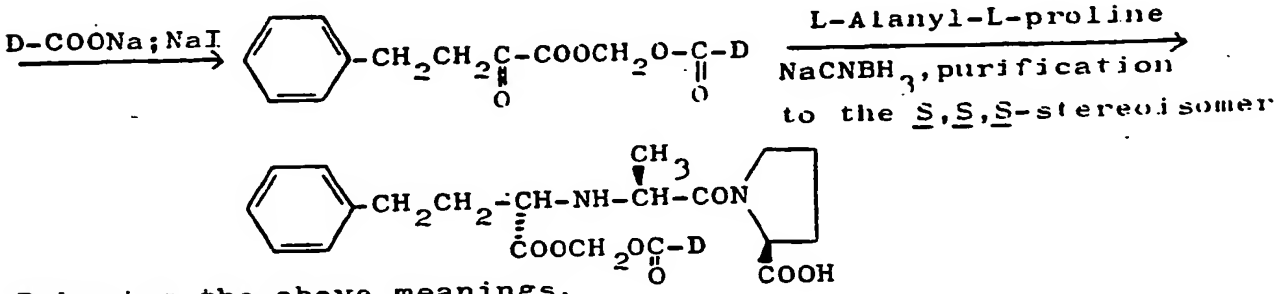


in which D and R^1 have the above meanings, and $-N$ (COO⁻) stands for



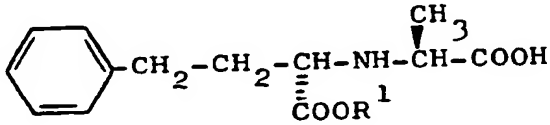
In another method, a compound of formula I, (with substructure Ib), in which R^2 is hydrogen, and R^1 = -A-O-C(=O)-D, A being $-CH_2-$, can be prepared in the following way:





D having the above meanings.

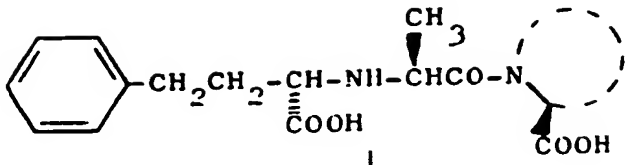
In still another method a compound of formula I can be prepared in the following way: A reactive derivative of a compound of formula IV having the S,S,-configuration



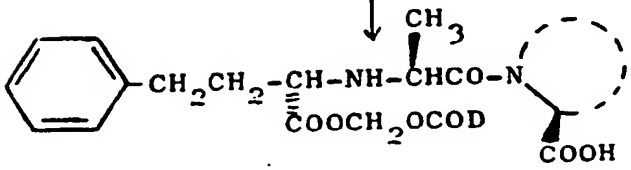
(IV)

is reacted with an ester of an amino acid of formula RH ($R^2 \neq H$) having the S-configuration, R^1 and R having the above meanings, to give the desired compound of formula I. For certain $R^2 \neq H$ the compounds of formula I can subsequently be transformed to compounds of formula I in which $R^2 = H$.

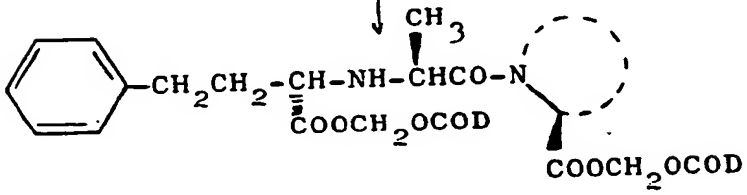
In a further method, a compound of formula I, in which -A- stands for $-CH_2-$ and R^1 and/or R^2 stands for DCOO- can be synthesized according to the following reaction scheme:



DCOOCH$_2$I ; 1 Mol base

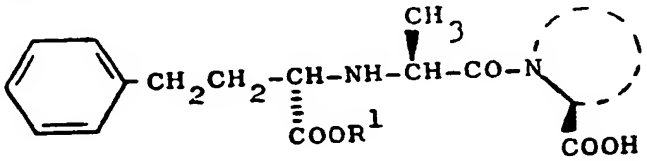


DCOOCH$_2$I ; 1 Mol base



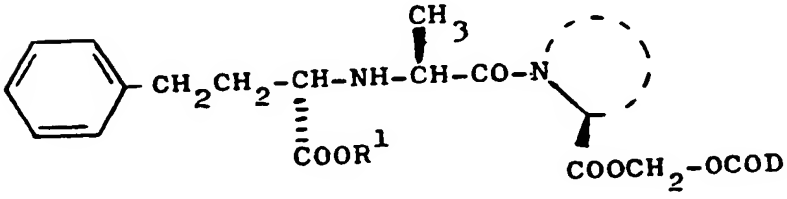
in which D and  have the above meanings.

In still a further method, a compound of formula I in which -A- is -CH_2- and R^2 is DCOOA-, can be prepared as follows:



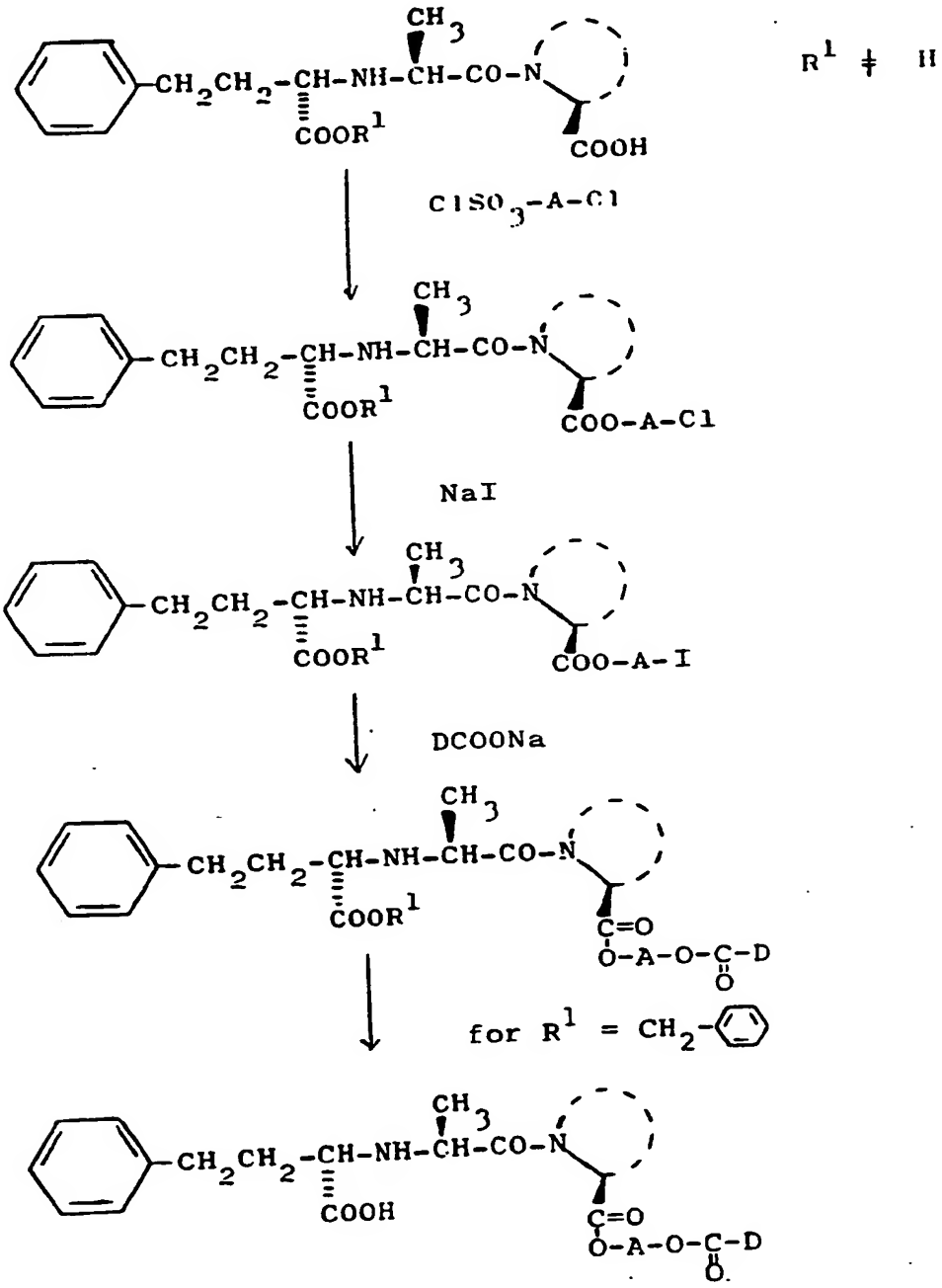
$R^1 \neq H$

DCOOCH$_2$I



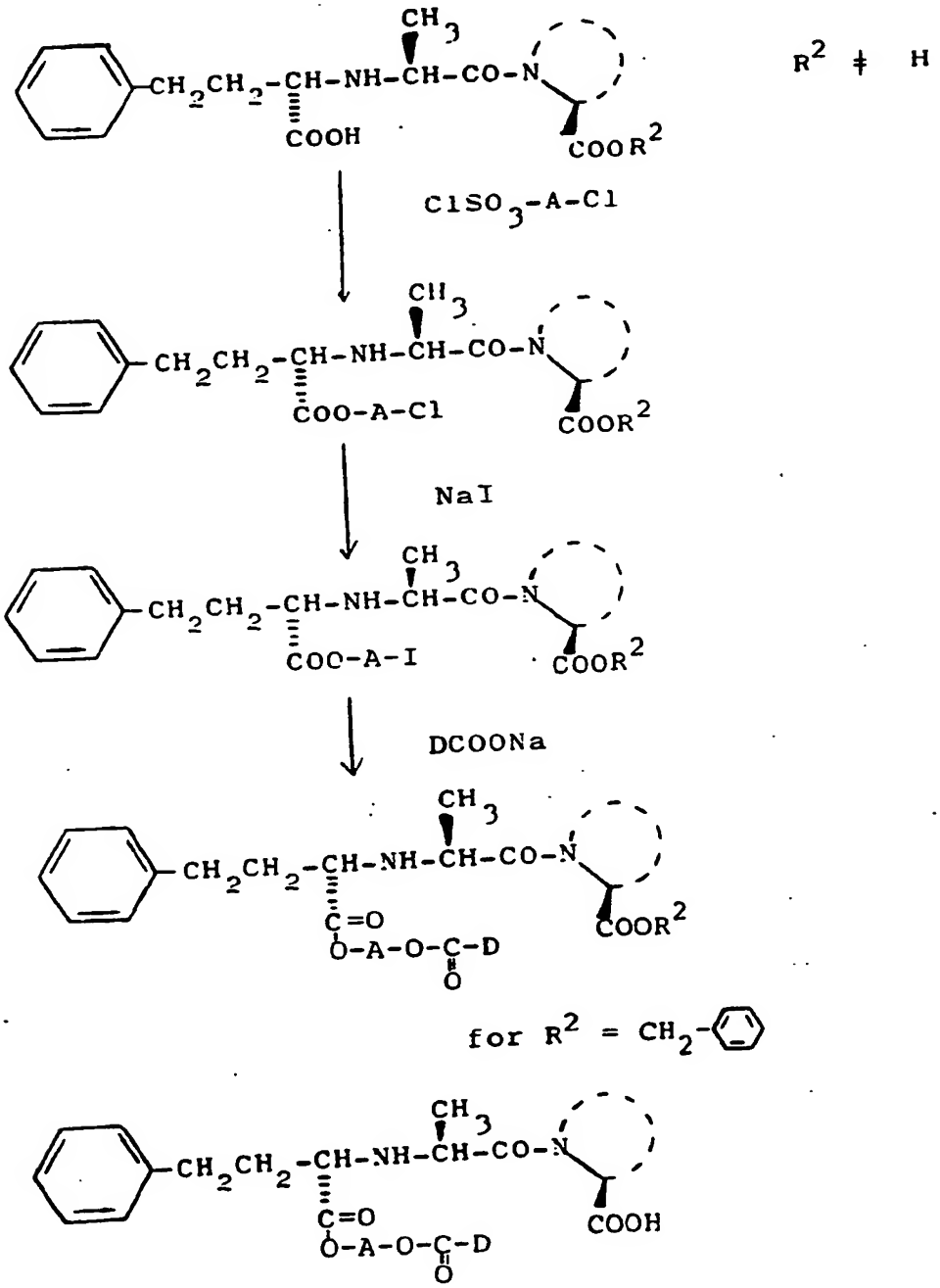
in which D has the above meanings, and R^1 has the above meanings except hydrogen.

In another method, a compound of formula I is produced according to the following reaction scheme:



A having the above meanings, and R^1 having the above meanings except hydrogen.

In still another method, a compound of formula I is produced according to the following reaction scheme:



A having the above meanings, and R^2 having the above meanings except hydrogen.

If, in any of the above preparations of compound I, a temperary protection of one or more functionalities in one of the starting materials, or intermediates, is appropriate, e.g. a protection of an amine. and/or a carboxyl function, protective groups (e.g. benzyloxy carbonyl, and/or benzyl groups) can be introduced at a suitable stage in the synthesis, e.g. in the starting materials, removal of the protection can take place later in the synthetic sequence, e.g. as the last step.

It is a further object of the invention to provide pharmaceutical compositions, including compounded compositions which are useful in the treatment of hypertension and congestive heart failure in the human and veterinary practice, and which may be used for enteral or parenteral administration, but preferably for oral use.

With this object in view, the compositions of the invention contain as an active component at least one compound of formula I or a salt thereof as defined together with solid, semisolid or liquid pharmaceutical carriers and/or diluents.

In the said compositions, the content of therapeutically active material in the carrier substances can vary between 1% and 95% by weight. The compositions can be worked up to various pharmaceutical forms of presentation, such as disintegrating, effervescent, or sustained-release tablets, pills, dragees, suppositories, capsules, powders, suspensions, and the like.

Pharmaceutically acceptable, non-toxic, organic or inorganic, solid, semisolid or liquid carriers and/or auxiliary agents can be used to make up compositions containing the present compounds. Gelatine, sugars and sugar alcohols, starches, starch derivatives, cellulose and cellulose derivatives, magnesium or calcium stearate, talc, naturally occurring or modified, vegetable and animal fats and oils, mineral oils, gums, polyalkylene glycols; polyvinyl derivatives, buffers, organic acids, carbonates, or other known carriers and/or auxiliary agents for medicaments are all suitable.

Furthermore, the compositions may contain other therapeutically active components which can appropriately be administered together with the present compounds, such as β-blocking agents, potassium chloride, potassium sparing diuretics, and antihypertensives etc. Such compounded compositions may be administered in mixtures or in forms where the active components are separated from each other, e.g. in multi-layer tablets.

Another object of the invention resides in the selection of a dose of the present compounds and a dosage unit of the compositions of the invention which dose and dosage unit can be administered so that the desired activity is achieved without simultaneous secondary effects. In the human therapy the present compounds are conveniently admini-

stered (to adults) in dosage units of the compositions containing not less than 0.5 mg and up to 100 mg, preferably from 1 mg to 50 mg.

By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents, carriers, solvents and/or auxiliary agents.

In the form of a dosage unit, the present compounds may be administered once or more times a day at appropriate intervals, always depending, however, on the condition of the patient, and in accordance with the prescription made by the medical practitioner.

Thus, a typical daily dose will be an amount of from 0.01 - 3 mg/kg body weight per day of the present compounds, preferably an amount of from 0.02 - 2 mg/kg body weight/day.

In the continuous therapy of patients, enteral administration forms such as disintegrating tablets, capsules, suspensions or the like are the appropriate forms, whereas in some instances, as mentioned above, sustained release formulations may be used as well.

In the veterinary practice the above pharmaceutical compositions may also be used, preferably in the form of

dosage units containing an amount of the present compounds calculated according to the weight of the animal in question.

Still another object of the invention is to provide a method of treating patients suffering from hypertension, and congestive heart failure, the method comprising administering to the patient an effective amount of the present compounds. The present compounds are typically administered in amounts of 0.01 - 3 mg/kg body weight of the patient/day, corresponding to, for adult human patients, from approximately 0.5-200 mg per day. The preferred dosage range is from 0.02 to 2 mg/kg body weight/day.

In the treatment of patients, the present compounds can be administered either alone or together with other therapeutically active compounds, as described above. Such combined treatment can be performed with formulations containing more or all of the therapeutically active compounds, or these may be administered in separate formulations, these being given simultaneously or with suitable intervals.

In the treatment of patients, the daily dose is administered either at one time, or in divided dosages, e.g. two, three or four times a day.

The invention will be further described in the following Preparation and Examples which are not to be construed as limiting the invention.

Preparation 1

(S)-Benzoxycarbonylproline, potassium salt, monohydrate

A suspension of (S)-benzoxycarbonylproline (25 g) in water (170 ml) is adjusted to pH 7.5 by addition of 1 N KOH while stirring. The resulting solution is evaporated *in vacuo*. The crystalline residue is triturated with acetone (100 ml) and thereafter the potassium salt is collected by filtration.

Preparation 2

Chloromethyl 3-ethylamino-4-phenoxy-5-sulfamoylbenzoate

3-Ethylamino-4-phenoxy-5-sulfamoylbenzoic acid (4.2 g), is dissolved in a mixture of methylene chloride (400 ml) and water (400 ml), containing sodium hydrogen carbonate (4.0 g), and tetrabutylammonium hydrogen sulfate (0.4 g). A solution of chloromethyl chlorosulfate (2.3 g) in methylene chloride (25 ml) is added dropwise while stirring at room temperature. Stirring is continued for 15 minutes, whereafter the two layers are separated. The aqueous layer is extracted with methylene chloride (50 ml). The combined methylene chloride phases are extracted with saturated aqueous sodium hydrogen carbonate solution (100 ml) and washed twice with water (2 x 100 ml). After drying over magnesium sulfate, petroleum ether is added to the filtrate to precipitate the crude title compound. After collection by filtration and recrystallization from chloroform-petroleum ether it is obtained with a melting point of 157 - 158°C.

Preparation 3

3-Ethylamino-4-phenoxy-5-sulfamoylbenzoyloxymethyl (S)--N-benzoxycarbonylprolinate

A mixture of chloromethyl 3-ethylamino-4-phenoxy--5-sulfamoylbenzoate (8.85 g), (S)-benzoxycarbonylproline, potassium salt, monohydrate (8.78 g), sodium iodide (8.62 g), and acetone (240 ml) is stirred in the dark for 6 days. Thereafter the reaction product is precipitated by slow addition of water (145 ml). After collection by filtration and drying in air, it is redissolved in boiling acetone (170 ml). The hot solution is filtered, and the pure compound precipitated by addition of water (10 ml) while cooling. After collection by filtration, it was obtained with a melting point of 164 - 165°C.

Preparation 4

Chloromethyl 4-phenoxy-3-propylamino-5-sulfamoylbenzoate

By replacing in preparation 2 3-ethylamino-4-phenoxy-5-sulfamoylbenzoic acid by an equimolar amount of 4-phenoxy-3-propylamino-5-sulfamoylbenzoic acid and following the procedure described, the title compound is obtained with a melting point of 169-170°C.

Preparation 5

3-Ethylamino-4-phenoxy-5-sulfamoylbenzoyloxymethyl (S)-prolinate, hydrochloride

A suspension of 3-ethylamino-4-phenoxy-5-sulfamoylbenzoyloxymethyl (S)-N-benzoxycarbonylprolinate (3.59 g) in a mixture of acetic acid (40 ml) and 4 N hydrochloric acid (3 ml) is shaken in a hydrogen atomosphere in the presence of palladium-on-carbon catalyst (0.25 g). The reaction is controlled by tlc-chromatography (silica gel plates; ethyl acetate: formic acid: water; 8:1:1 ; visualization 254 and 360 nm), the reaction product showing an rf-value of 0.35.

After completion of the reaction, the catalyst is removed by filtration, and the filtrate is evaporated *in vacuo*. The residue is triturated with diethyl ether resulting in crude amorphous hydrochloride, which is crystallized by standing in ethyl acetate (100 ml), isolated by filtration, and dried in air.

Preparation 6

Chloromethyl 4-chloro-2-furfurylamino-5-sulfamoylbenzoate

A solution of chloromethyl chlorosulfate (3.64 ml) in methylene chloride (200 ml) is added to a stirred mixture of methylene chloride (640 ml) and water (640 ml), containing 4-chloro-2-furfurylamino-5-sulfamoylbenzoic acid (13.28 g), sodium hydrogen carbonate (11.52 g) and tetrabutylammonium hydrogen sulfate (0.70 g). Addition

is complete after 30 minutes, and stirring at 30°C is continued for 4 hours. The aqueous layer is extracted with methylene chloride (200 ml). The total methylene chloride solution is dried over magnesium sulfate, charcoaled and filtered. The filtrate volume is reduced to 100 ml *in vacuo*, and petroleum ether (1000 ml) is gradually added to precipitate the chloromethyl ester. It is collected by filtration and washed with petroleum ether. Melting point: 166-168°C (dec.).

Preparation 7

Iodomethyl 4-chloro-2-furfurylamino-5-sulfamoylbenzoate

Chloromethyl 4-chloro-2-furfurylamino-5-sulfamoylbenzoate (11.4 g) is added to a solution of sodium iodide (4.05 g) in dry acetone (60 ml). The mixture is stirred overnight at room temperature. Chloroform (150 ml) is added, and the mixture is partially evaporated *in vacuo*; the process is repeated with further chloroform (150 ml) to displace acetone. The resulting suspension is extracted with water (200 ml). The chloroform layer is dried over magnesium sulfate, charcoaled and filtered. The filtrate volume is reduced *in vacuo* to 100 ml, and petroleum ether (750 ml) is gradually added to cause crystallization of the title compound which is filtered off and washed with petroleum ether. Melting point: 131-132°C.

Preparation 8

Chloromethyl 4-phenoxy-3-(1-pyrrolidino)-5-sulfamoyl-benzoate

4-Phenoxy-3-(1-pyrrolidino)-5-sulfamoylbenzoic acid (1.65 g) was dissolved in a mixture of methylene chloride (90 ml) and water (90 ml), containing sodium hydrogen carbonate (1.52 g), and tetrabutylammonium hydrogen sulfate (0.15 g).

A solution of chloromethyl chlorosulfate (0.86 g) in methylene chloride (20 ml) was added dropwise while stirring at 5°C. Stirring was continued for 15 minutes and for 3 hours at room temperature, whereafter the two layers were separated. The aqueous layer was extracted with methylene chloride (50 ml). The combined methylene chloride phases were extracted with freshly prepared, saturated aqueous sodium hydrogen carbonate solution (70 ml), washed twice with water (2 x 70 ml) and with saturated aqueous sodium chloride solution (70 ml).

After drying over magnesium sulfate, petroleum ether was added to the filtrate, to precipitate the crude title compound. It was purified by flash chromatography on silica gel 60 (230 - 400 mesh) (Merck (RTM)) at 1.5 bar nitrogen with an eluent consisting of methylene chloride: ethyl-acetate (98:4).

The fractions were analyzed by TLC, and the fractions containing the title compound, (Rf: 0.26, on a silica gel 60 F-254 plate (Merck) with the same eluent as used for the flash chromatography, and visualized by UV (254 and 360

nm)), were combined and evaporated in vacuo.

After recrystallization of the residue from acetone-petroleum ether, the title compound was obtained with a melting point of 171-171.5°C.

Preparation 9

Benzyl (S,S,S)-N-[1-(4-phenoxy-3-propylamino-5-sulfamoyl-benzoyloxy)-methoxycarbonyl-3-phenylpropyl]-alanyl-prolinate

Chloromethyl 4-phenoxy-3-propylamino-5-sulfamoyl-benzoate (2.2 g) was dissolved in dry acetone (100 ml), sodium iodide (0.9 g) was added, and the mixture was stirred for 5 hours at room temperature. Then ethyl diisopropylamine (0.71 g) and a solution of benzyl (S,S,S)-N-(1-carboxy-3--phenylpropyl)-alanylprolinate * (2.5 g) in acetone (300 ml) was added, and the stirring continued for 5 days at 35 - 40°C.

After evaporation in vacuo the residue was treated with a mixture of diethyl ether (50 ml) and ethyl acetate (100 ml). The precipitated sodium halogenides and ethyl diisopropylammonium halogenides were removed by filtration after cooling of the mixture for 2 hours. The salt mixture was washed with ethyl acetate.

The ethyl acetate was joined with the filtrate and washed with water (3 x 100 ml) and with saturated sodium chloride (100 ml). Precipitated benzyl (S,S,S)-N-(1--carboxy-3-phenylpropyl)-alanylprolinate * was filtered off, and the filtrate was dried over magnesium sulfate and

*U.S.Patent No. 4,374,829

evaporated in vacuo.

The residue was flash chromatographed, twice, on silica gel 60 (230 - 400 mesh) (Merck) at 1.5 bar nitrogen with an eluent consisting of methylene chloride: ethyl acetate (65:35).

The fractions were analyzed by TLC, with the same eluent as used for the flash chromatography and visualized by UV (254 and 360 nm). The fractions containing the title compound with a Rf value: 0.33 on a silica gel 60 F-254 plate (Merck) were combined and evaporated in vacuo.

The title compound was obtained as a colourless amorphous powder.

The proton NMR-spectrum ($(CD_3)_2SO$) showed signals at δ = 0.65 (3H, t, J=7), 1.04 (3H, d, J=7), 1.15-1.50 (2H, m), 1.6-2.3 (6H, m), 3.0 (2H, q), 3.5 (2H, m), 4.4 (1H, m), 5.08 (2H, s), 6.00 (2H, s), 6.8 (2H, d), 6.95-7.5 (4H, m), 7.33 (5H, s), 7.73 (1H, d).

Preparation 10

Benzyl (S,S,S)-N-[1-(4-phenoxy-3-(1-pyrrolidyl)-5-sulfamoylbenzoyloxy)-methoxycarbonyl-3-phenylpropyl]-alanyl-prolinate

Chloromethyl 4-phenoxy-3-(1-pyrrolidyl)-5-sulfamoyl-benzoate (328 mg) was dissolved in dry acetone (20 ml), sodium iodide (132 mg) was added, and the mixture stirred for 3 hours at room temperature. Precipitated sodium chloride was not removed from the mixture. Then ethyl diisopropylamine (103 mg) and benzyl (S,S,S)-N-(1-carboxy-

3-phenylpropyl)-alanylprolinate * (350 mg) was added, and the mixture was stirred at 35 - 40°C for 2 days.

After evaporation in vacuo the residue was treated with ethyl acetate (10 ml) to crystallize a mixture of sodium halogenides and ethyl diisopropylammonium halogenides by standing in the refrigerator overnight. The salt mixture was removed by filtration and washed with ethyl acetate. The ethyl acetate was combined with the filtrate and washed with water (3 x 10 ml) and saturated sodium chloride solution (10 ml). After drying over magnesium sulfate, the filtrate was evaporated in vacuo.

The pale yellow residue was flash chromatographed, twice, on silica gel 60 (230 - 400 mesh) (Merck) at 1.5 bar nitrogen with an eluent consisting of methylene chloride: ethyl acetate (65:35).

The fractions were analyzed by TLC with an eluent consisting of methylene chloride: ethyl acetate (60:40) and visualized by UV (254 and 360 nm). The fractions containing the title compound (Rf = 0.24 on a silica gel 60 F-254 plate (Merck)) were combined and evaporated in vacuo to yield the title compound as a straw coloured, amorphous powder.

The proton NMR-spectrum ($(CD_3)_2CO$) showed signals at δ = 1.15 (d, 3H), 1.6-2.9 (m,12H), 3.2-3.8 (m, 8H), 4.50 m, 1H), 5.11 (s, 2H), 6.06 (s, 2H), 6.42 (s, 2H), 6.7-7.5 (m, 16H), 7.65 (d, J=2, 1H), 8.01 (d, J=2, 1H).

* U.S. Patent No. 4,374,829

Preparation 11

Benzyl (S,S)-N-[N-[1-carboxy-3-phenylpropyl]-alanyl]-N--(indan-2-yl)-glycinate, hydrochloride

Thionyl chloride (5.4 g) was added to benzyl alcohol (38 ml) at approx. -5°C, during 10 minutes, with stirring. After stirring for another 5 minutes at approx. -5°C, (S,S)--N-[N-[1-carboxy-3-phenylpropyl]-alanyl]-N-(indan-2-yl)--glycine (4.4 g) was added in portions, during 15 minutes, at -5°C to -10°C. The cooling bath was then removed, and stirring was continued at room temperature for 24 hours to yield the title compound in solution as a reaction mixture which was used in Preparation 12 without further purification.

Preparation 12

Benzyl (S,S)-N-[N-benzyloxycarbonyl-N-[1-carboxy-3-phenylpropyl]-alanyl]-N-(indan-2-yl)-glycinate

To the reaction mixture of Preparation 11, containing benzyl (S,S)-N-[N-[1-carboxy-3-phenylpropyl]-alanyl]-N--(indan-2-yl)-glycinate, hydrochloride, was added chloroform (100 ml), benzyloxy carbonyl chloride (2.6 g) and saturated aqueous sodium bicarbonate solution (50 ml). The mixture was stirred for two hours at approx. 25°C, during which period the pH was monitored by means of a pH-meter, and kept at a pH of approx. 8.5 by the appropriate addition of 2N aqueous sodium hydroxide solution. The reaction mixture was then acidified to pH 2.0 with 4 N aqueous hydrochloric acid, and the phases were separated. The aqueous phase was extracted

once with chloroform (25 ml), and the combined chloroform phases were extracted once with water (25 ml), dried with magnesium sulfate and evaporated *in vacuo*. The residue was flash chromatographed on a silica gel 60 (230-400 mesh) column, using as eluent first diethyl ether: petroleum ether (1:1), then methylene chloride: petroleum ether: ethyl acetate: acetic acid (70:25:5:0.5). The fractions containing the desired compound were combined and evaporated *in vacuo* to yield the title compound as an amorphous material.

100 MHz ^{1}H-NMR ($CDCl_3$, tetramethylsilane δ = 0): 1.10 (m, 3H), 1.90 (m, 1H), 2.25-3.50 (m, 7H), 3.75 (m, 1H), 3.65 (d, J=17, 1H), 4.30 (d, J=17, 1H), 4.60-5.40 (m, 6H), 7.0-7.5 (m, 20H).

Preparation 13

Benzyl (S,S)-N-[N-benzyloxycarbonyl-N-[1-chloromethoxy-carbonyl-3-phenylpropyl]-alanyl]-N-(indan-2-yl)glycinate

To a solution of benzyl (S,S)-N-[N-benzyloxycarbonyl--N-[1-carboxy-3-phenylpropyl]-alanyl]-N-(indan-2-yl)-glycinate (3.0 g), sodium hydrogen carbonate (1.7 g) and tetrabutylammonium hydrogen sulfate (0.16 g) in a mixture of water (12 ml) and methylene chloride (12 ml) was added a solution of chloromethyl chlorosulfate (0.55 ml) in methylene chloride (1 ml) at 20°C, with stirring, and the mixture was stirred for 1 1/2 hours. Methylene chloride (50 ml) was added, and after separation the methylene chloride phase was washed with water (10 ml), dried with magnesium sulfate and evaporated *in vacuo*. The residue was subjected

to flash chromatography on a silica gel-60 (230-400 mesh) column, using a mixture of methylene chloride and ethyl acetate (98:2) as eluent. The appropriate fractions were combined and evaporated to yield the title compound as an oil.

100 MHz ^{1}H-NMR ($CDCl_3$, tetramethylsilane δ = 0): 1.25 (m, 3H), 2.00 (m, 1H), 2.30-3.40 (m, 7H), 3.70 (d, J=18, 1H), 4.00 (d, J=18, 1H), 4.33 (m, 1H), 5.15 (m, 4H), 4.9-5.8 (m, 4H), 7.0-7.5 (m, 19H).

Preparation 14

Benzyl (S,S)-N-[N-benzyloxycarbonyl-4-[1-iodomethoxycarbonyl-3-3-phenylpropyl]-alanyl]-N-(indan-2-yl)-glycinate

A solution of sodium iodide (1.85 g) in acetone (13 ml) was added to a solution of benzyl (S,S)-N-[N-benzyloxycarbonyl-N-[1-chloromethoxycarbonyl-3-phenylpropyl]-alanyl]-N-(indan-2-yl)-glycinate (0.43 g) in acetone (13 ml), and the mixture was stirred for 20 hours. It was then evaporated *in vacuo*, and the residue was treated with methylene chloride (15 ml), filtered and evaporated *in vacuo* to yield the title compound as a syrup.

100 MHz ^{1}NMR ($CDCl_3$, tetramethylsilane δ = 0): 1.25 (m, 3H), 2.00 (m, 1H), 2.4-3.4 (m, 7H), 3.70-4.20 (d, ABq, 2H), 4.30 (m, 1H), 4.9-5.6 (m, 6H), 5.80 (m, 2H), 7.10-7.50 (m, 19H).

Preparation 15

Benzyl (S,S,S)-N-benzyloxycarbonyl-N-[1-carboxy-3-phenyl-

propyl-alanylprolinate

Benzyl (S,S,S)-N-[1-carboxy-3-phenylpropyl]-alanyl-prolinate * (4.2 g) was dissolved in a mixture of chloroform (40 ml) and triethylamine (2.6 ml). Benzyloxycarbonyl-chloride (1.5 ml) was added with stirring. After 1 1/2 hour additional triethylamine (0.6 ml) and benzyloxycarbonyl-chloride (0.4 ml) was added. Stirring was continued for 1 hour more, after which water (20 ml), followed by 1 M aqueous phosphoric acid (20 ml) was added. The water phase was extracted with chloroform (20 ml), and the combined chloroform phases were washed twice with water (2 x 10 ml), dried with magnesium sulfate and evaporated in vacuo. The residue was flash chromatographed on a silica gel 60 (230-400 mesh) column using a mixture of petroleum ether, ethyl acetate and acetic acid (50:50:0.5) as an eluent. The appropriate fractions were combined and evaporated in vacuo to yield the title compound as a syrup.

100 MHz ^{1}H-NMR ($CDCl_3$, tetramethylsilane δ = 0): 1.07 (m, 3H), 1.8-2.2 (m, 4H), 2.5-4.0 (m, 7H), 4.5-5.0 (m, 2H), 5.0-5.35 (m, 4H), 7.0-7.5 (m, 16H).

Preparation 16

Benzyl (S,S,S)-N-benzyloxycarbonyl-N-[1-chloromethoxy-carbonyl-3-phenylpropyl]-alanylprolinate

By following the procedure of Preparation 13, except that in the eluent the ratio between methylene chloride and ethylacetate was 95:5, and by replacing benzyl (S,S)-N-[N--benzyloxocarbonyl-N-[1-carboxy-3-phenylpropyl]-alanyl]-N-

* U.S. Patent No. 4,374,829

-(indan-2-yl)-glycinate with benzyl (S,S,S)-N-benzyloxycarbonyl-N-[1-carboxy-3-phenylpropyl]-alanylprolinate, the title compound was obtained as an oil.

100 MHz ^{1}H-NMR ($CDCl_3$, tetramethylsilane δ = 0): 1.22 (d, J=7, 3H), 1.8-2.2 (m, 5H), 2.2-2.9 (m, 3H), 3.3-3.9 (m, 3H), 4.40 (m, 2H), 5.0-5.7 (m, 6H), 7.0-7.4 (m, 15H).

Preparation 17

Benzyl (S,S,S)-N-benzyloxycarbonyl-N-[1-iodomethoxycarbonyl-3-phenylpropyl]-alanylprolinate

By following the procedure of Preparation 14, and by replacing (S,S)-N-[N-benzyloxycarbonyl-N-[1-chloromethoxycarbonyl-3-phenylpropyl]-alanyl N-(indan-2-yl)-glycinate with benzyl (S,S,S)-N-benzyloxycarbonyl-N-[1-chloromethoxycarbonyl-3-phenylpropyl]-alanylprolinate, the title compound was obtained as an oil.

100 MHz ^{1}H-NMR ($CDCl_3$, tetramethylsilane δ = 0): 1.22 (d, J=6, 3H), 1.8-2.3 (m, 5H), 2.3-2.8 (m, 3H), 3.3-3.9 (m, 2H), 4.1-4.5 (m, 2H), 4.9-5.3 (m, 4H), 5.70, (bs 2H), 7.0-7.4 (m, 15H).

Example 1

3-Ethylamino-4-phenoxy-5-sulfamoylbenzoyloxymethyl(S,S,S)-N-(1-carbethoxy-3-phenylpropyl)alanylprolinate, hydrochloride

To a chilled solution of (S,S)-N-(1-carbethoxy-3-phenylpropyl)alanine (1.4 g), 3-ethylamino-4-phenoxy-5-sulfamoylbenzoyloxymethyl-(S)-prolinate, hydrochloride

(2.4 g), and hydroxybenztriazole (0.74 g) in dimethylformamide (20 ml), N,N-dicyclohexylcarbodiimide (1.03 g) is added in small portions while stirring. Thereafter the reaction mixture is allowed to reach room temperature. After stirring for 5 hours, the reaction mixture is filtered, and the filtrate evaporated in vacuo. The residue is purified by flash chromatography on silica gel eluting with ethyl acetate: ethanol: acetic acid (90:10:0.5). The eluates are analyzed by TLC-chromatography (ethyl acetate: formic acid: water (8:1:1). The fractions showing the spot with an Rf-value of 0.74 are combined and evaporated in vacuo. The residue is dissolved in ethyl acetate containing 2% of water. 4 N Hydrochloric acid (2.5 ml) is added, and thereafter the solvents are removed by evaporation in vacuo. The residue is triturated with diethyl ether, and the resulting amorphous title compound is filtered off and dried in air.

The proton NMR-spectrum ($(CD_3)_2SO + D_2O$) showed signals at δ = 3.1 (2H, q), 4.45 (1H, m), 5.95 (2H, bs), 7.4 (1H, d), 7.69 (1H, d). Tetramethylsilane was used as internal reference.

Example 2

(S,S,S)-N-[1-[(4-Chloro-2-furfurylamino-4-sulfamoyl-benzoyloxy)methoxycarbonyl]-3-phenylpropyl]-alanylproline

A solution of (S,S,S)-N-[1-carboxy-3-phenylpropyl] -alanylproline (0.92 g), and sodium hydroxide (0.1 g) in water (125 ml) is evaporated to dryness in vacuo. The

residue is dried by azeotropic distillation with ethyl methyl ketone in vacuo. The resulting sodium salt is dissolved in dimethylformamide (100 ml). Iodomethyl 4-chloro-2-furfurylamino-5-sulfamoylbenzoate (1.18 g) is added, and the mixture is stirred for three hours at 20°C. The solvent is removed in vacuo (0.5 mmHg) at 20°C. The residue is partitioned between water (100 ml) and ethyl acetate (100 ml). The ethyl acetate layer is extracted with water (25 ml) followed by saturated sodium choride solution (10 ml), dried with magnesium sulfate and evaporated in vacuo. The residue is purified by flash chromatography on silica gel 60 (230 - 400 mesh) (Merck) at 1.5 bar nitrogen with an eluent consisting of ethyl acetate: ethanol: acetic acid (80:20:0.5).

The fractions are analyzed by TLC, and the fractions containing the title compound (Rf = 0.32 on a silica gel 60 F-254 plate (Merck), with the same eluent as used for the flash chromatography, and visualized by UV (254 and 360 nm)) are combined and evaporated in vacuo. The residue is dissolved in ethyl acetate (25 ml), filtered through Dicalite® and evaporated. The residue is treated with ethyl ether (10 ml) and filtered to yield the title compound as an amorphous powder.

The proton NMR-spectrum ($(CD_3)_2CO + D_2O$) showed signals at δ = 1.20 (3H, d), 2.7 (2H, t), 3.35 (1H, t), 4.4 (1H, m), 4.66 (2H, s), 6.05 (2H, bs), 7.15 (1H, s), 8.56 (1H, s). Tetramethylsilane was used as internal reference.

Example 3

4-Chloro-2-furfurylamino-5-sulfamoylbenzoyloxymethyl (S,S,S)-N-[1-[(4-chloro-2-furfurylamino-5-sulfamoylbenzoyloxy)methoxycarbonyl]-3-phenylpropyl]-alanylprolinate

A solution of (S,S,S)-1-N-[1-carboxy-3-phenylpropyl]-alanylproline (0.186 g) and sodium hydroxide (0.040 g) in water (25 ml) is evaporated to dryness in vacuo. The residue is dried by azeotropic distillation with ethyl methyl ketone in vacuo. The resulting di-sodium salt is dissolved in dimethyl formamide (30 ml) and cooled to 3°C. Iodomethyl 4-chloro-2-furfurylamino-5-sulfamoylbenzoate (0.471 g) is added, and the mixture is stirred with ice-cooling for one hour and at 20°C for one hour. The solvent is removed in vacuo (0.1 mmHg) at 20°C. The residue is partitioned between water (25 ml) and ethyl acetate (25 ml). The ethyl acetate layer is extracted with water (10 ml) followed by saturated sodium chloride solution (2 ml), dried with magnesium sulfate, and evaporated in vacuo. The residue is purified by flash chromatography on silica gel 60 (230 - 400 mesh) (Merck) at 1.5 bar nitrogen with an eluent consisting of methylene chloride: ethyl acetate (1:1).

The fractions are analyzed by TLC, and the fractions containing the title compound (Rf = 0.47 on a silica gel 60 F-254 plate (Merck), with an eluent consisting of methylene chloride: ethyl acetate (1:3), and visualized by UV (254 and 360 nm)) are combined and evaporated in vacuo to yield the title compound as a syrup.

The proton NMR-spectrum ($CDCl_3$ + D_2O) showed

signals at δ = 3,29 (1H, t), 4.41 (4H, m), 5.93 (4H, bs), 6.3 (4H, m), 7.37 (2H, m), 8.53 (1H,s), 8.56 (1H, s). Tetramethylsilane was used as internal reference.

Example 4

(S,S,S,S,S)-2-[N-[1-(4-phenoxy-3-propylamino-5-sulfamoyl-benzoyloxymethoxycarbonyl)-4-phenylpropyl]-alanyl]-2--azabicyclo 3.3.0 octane-3-carboxylic acid

By following the procedure of Example 2, but replacing iodomethyl 4-chloro-2-furfurylamino-5-sulfamoyl-benzoate by an equimolar amount of iodomethyl 4-phenoxy--3-propylamino-5-sulfamoylbenzoate (prepared from the corresponding chloromethyl ester of Preparation 4 by reaction with excess of potassium iodide in acetone and subsequent precipitation of the iodomethyl ester by dilution with chilled water), and (S,S,S)-N(1-carboxy-3-phenyl-propyl)-alanylproline by an equimolar amount of (S,S,S,S,S)--2-[N-(1-carboxy-3-phenylpropyl)-alanyl]-2-azabicyclo[3.3.0] octane-3-carboxylic acid, the title compound was obtained as a white amorphous substance.

Example 5

(S,S,S)-N-[1-(4-phenoxy-3-propylamino-5-sulfamoylbenzoyl-oxy)-methoxycarbonyl-3-phenylpropyl]-alanylproline

A solution of benzyl (S,S,S)-N-[1-(4-phenoxy-3--propylamino-5-sulfamoylbenzoyloxy)-methoxycarbonyl-3--phenylpropyl]-alanylprolinate (1.4 g) in ethyl acetate (80 ml) was shaken in a hydrogen atmosphere in the presence of

10% palladium-on-carbon catalyst (0.4 g). After 2 hours the hydrogen uptake had ceased, the catalyst was removed by filtration, and the filtrate was evaporated in vacuo.

The completion of the reaction had been controlled by TLC on a silica gel 60 F-254 plate (Merck) with the eluent ethyl acetate: ethanol: acetic acid (90:10:0.5), visualized by UV (254 and 360 nm). Rf value: 0.18.

The residue of the evaporation was triturated with petroleum ether to give the title compound as a colourless, amorphous powder, which was isolated by filtration. Mass-FAB-spectrum: $(M+H)^+$ m/z 711, $(M+K)^+$ m/z 749.

The proton NMR-spectrum ($(CD_3)_2CO$ showed signals at δ = 0.74 (3H, t, J=7), 1.17 (3H, d, J=7), 1.15-1.65 (2H, m), 2.7 (2H, t), 3.15 (2H, q), 3.3-3.85 (4H, m), 4.5 (1H, m), 6.07 (2H, s), 6.6 (2H, bs), 6.8-7.5 (5H, m), 7.2 (5H, s), 7.55 (1H, d, J=2), 7.89 (1H, d, J=2).

Example 6

(S,S,S)-N-[1-[4-phenoxy-3-(1-pyrrolidyl)-5-sulfamoylbenzoyloxy]-methoxycarbonyl-3-phenylpropyl]-alanylproline

A solution of benzyl (S,S,S)-N-[1-[4-phenoxy-3-(1-pyrrolidyl)-5-sulfamoylbenzoyloxy]-methoxycarbonyl-3-phenylpropyl]-alanylprolinate (115 mg) in ethyl acetate (15 ml) was shaken in a hydrogen atmosphere in the presence of 10% palladium-on-carbon catalyst (30 mg).

The reaction was controlled by TLC on a silica gel 60 F-254 plate (Merck), with the eluent ethyl acetate: ethanol: acetic acid (90:10:0.5) visualized by UV (254 and 360 nm),

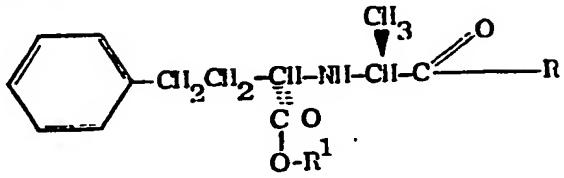
Rf-value of the title compound: 0.19.

After completion of the reaction, the catalyst was removed by filtration, and the filtrate was evaporated in vacuo. The residue was triturated with petroleum ether to give the title compound as a straw coloured amorphous powder. It was isolated by filtration and dried in vacuo (0.07 mmHg) for 2 hours.

The proton NMR-spectrum ($(CD_3)_2CO$ showed signals at δ = 1.17 (3H, d), 2.7 (2H, t), 3.15-3.9 (8H, m), 4.5 (1H, m), 6.07 (2H, s), 6.5 (2H, bs), 6.77 (2H, d, J=7), 6.9-7.5 (3H, m), 7.2 (5H, s), 7.65 (1H, d, J=2), 7.99 (1H, d, J=2).

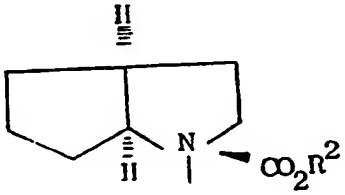
CLAIMS:

1. A compound of the general formula I:

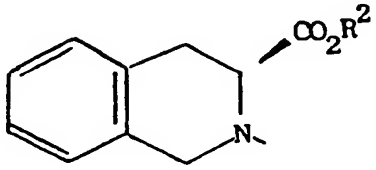


(I)

in which the asymmetric centers all have the S-configuration, and in which R stands for

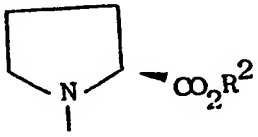


(Ia)

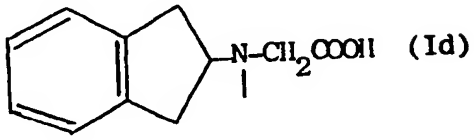


(Ic)

or



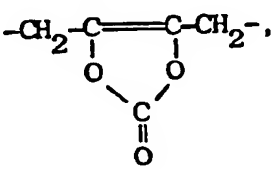
(Ib)



(Id)

and R^1 and R^2, which can be the same or different, each stands for hydrogen, lower alkyl, aryl-lower alkyl, or -A-O-C(=O)-D;

provided that at least one of R^1 or R^2 is -A-O-C(=O)-D; where A stands for $-CH(R^3)-$, $-CH_2-CH(OH)-CH_2-$, or



where R^3 is hydrogen, lower alkyl or aryl-lower alkyl; lower alkyl stands for straight or branched C_1-C_6-alkyl, aryl stands

for unsubstituted or substituted phenyl or naphthyl, and

D-C-O- stands for the radical of a carboxy group containing

compound (D-COOH) with diuretic and/or saluretic activity, and salts thereof.

2. The invention substantially as described.

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